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Tobacco and non-Hodgkin's lymphoma: combined analysis of three case-control studies (United States)

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The role of tobacco in the etiology of non-Hodgkin's lymphoma (NHL) was evaluated in a combined analysis of data from three population-based case-control studies conducted in four midwestern states of the United States: Nebraska, Iowa, Minnesota, and Kansas. Interviews were obtained from 1,177 cases (993 men, 184 women) and 3,625 controls (2,918 men, 707 women) or, if deceased, from their next-of-kin. Overall, there was no association between NHL and tobacco use (odds ratio [OR] = 1.0, 95 percent confidence interval [CI] = 0.8-1.1) or cigarette smoking (OR = 1.0, CI = 0.8-1.1). A slight negative association evident in analyses by intensity and duration of smoking was not present when interviews from proxy respondents were eliminated. There was a suggestion of a positive association between smoking and NHL among women (OR = 1.3, CI = 0.9-1.9), although there was no clear exposure-response relationship. This large case-control analysis provides no evidence that smoking is linked to the development of NHL among men. The possible role of smoking in the etiology of NHL among women needs further evaluation. *Cancer Causes and Control* 1997, 8, 159-166

Key words: Case-control studies, non-Hodgkin's lymphoma, smoking, tobacco, United States.

Introduction

Historically, non-Hodgkin's lymphoma (NHL) has not been considered a tobacco-related malignancy. Most studies have shown little or no association between NHL and smoking.[1-9] Two recent studies,[10,11] however, were more supportive of an association. A population-based case-control study of men in Iowa and Minnesota (United States) observed a 40 percent increased risk of non-Hodgkin's lymphoma among smokers with a two- to threefold increase for high grade and unclassified non-Hodgkin's lymphoma.[10] Risk increased with duration of smoking, but not intensity. A cohort study of policy-holders of the Lutheran Brotherhood Insurance Society[11] reported smokers having a twofold elevation in mortality from NHL, with an almost fourfold elevated risk among heavy smokers. No information on cell type or duration of smoking was available. In addition, the growing

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consensus that cigarette smoking is related causally to leukemia has suggested the need to reevaluate its role in the etiology of other hematopoietic and lymphatic malignancies, although the evidence is strongest for myeloid, not lymphoid, leukemia.[12-16]

To examine the role of tobacco in the etiology of NHL, we combined data from three population-based case-control studies conducted in four midwestern US states, including the population previously reported by Brown *et al.*[10] The combined dataset provided the large number of subjects required to evaluate the anticipated low level risks and to focus analyses on the high-risk subgroups suggested by the earlier research.

Materials and methods

The three population-based case-control studies combined for this reanalysis were conducted in Nebraska, Iowa/Minnesota, and Kansas. Detailed descriptions of the methods for each study have been published elsewhere.[5,10,17-24] Each study included several lymphatic and hematopoietic malignancies and, in Kansas only, soft tissue sarcoma. The studies in Iowa/Minnesota and Kansas included only White men, while the Nebraska study included both White men and White women. This report will evaluate NHL among White men and women.

Cases

In Nebraska, all cases of NHL among White men and women, age 21 years or older, residing in the 66 counties of eastern Nebraska, and diagnosed between 1 July 1983 and 30 June 1986, were identified through the Nebraska Lymphoma Study Group and area hospitals (n = 227 men, 214 women)(Table 1). In the Iowa/Minnesota study, all newly diagnosed cases of NHL among White men, aged 30 years or older, were ascertained from Iowa State Health Registry records and a special surveillance of Minnesota hospital and pathology laboratory records (n = 780). The diagnosis period for eligibility was March 1981 through October 1983 in Iowa, and October 1980 through September 1982 in Minnesota. In Minnesota, cases who resided in the cities of Minneapolis, St. Paul, Duluth, or Rochester at the time of diagnosis were excluded because agricultural exposures were the primary focus of the original investigations. In Kansas, all cases of NHL among White men, aged 21 years or older, diagnosed from 1979 through 1981, were identified through the University of Kansas Cancer Data Service, a registry covering the state of Kansas. A random sample of 200 men was drawn from the 297 NHL cases diagnosed in Kansas during the eligible time period.

Tumor tissue from the cases was reviewed by expert pathologists and classified according to the Working Formulation.[25-27] Analyses of follicular (Working Formulation categories B-D), diffuse (Working Formulation categories E-G), small lymphocytic (Working Formulation category A), and other (Working Formulation categories H-J and miscellaneous) NHL are presented. Only histologically confirmed cases were included. The number of confirmed cases was 426 (220 men, 206 women) in Nebraska and 172 in Kansas. In Iowa/Minnesota, the

Table 1. Number of non-Hodgkin's lymphoma cases and controls, response rates, and study methods in the case-control studies in Nebraska, Kansas, and Iowa/Minnesota

	Nebraska		Kansas	Iowa/Minnesota
	Men	Women	Men	Men
Cases identified	227	214	200	780
Histologically confirmed	220	206	172	—[a]
Interviewed	201	184	170	622
Interview response rate	91%	89%	96%[b]	89%
Controls identified	831	824	1,005	1,543
Interviewed	725	707	948	1,245
Interview response rate	87%	86%	94%	81%
Overall control response rate[c]	85%	84%	90%	78%

[a] Pathology review occurred after the interviews were conducted. Cases who were not interviewed did not undergo pathology review.

[b] The 96 percent response rate was based on 170 interviews out of 172 confirmed non-Hodgkin's lymphoma cases initially diagnosed as non-Hodgkin's lymphoma and five non-Hodgkin's lymphoma cases initially diagnosed as other cancer types in the study (*e.g.*, Hodgkin's disease).

[c] Overall control response rates account for the response rates in the initial household census and the interview response rates.

pathology review occurred after the interviews were obtained from cases. Because cases who were not interviewed did not undergo pathology review, the total number of eligible, histologically-confirmed cases cannot be determined.

Controls

Controls were selected randomly from the same geographic areas as cases, with frequency matching by race, gender, five-year age group, and vital status at the time of the interview. For living cases under age 65, controls were selected by two-stage random digit dialing (RDD).[28] For living cases aged 65 or older, controls were selected from the Health Care Financing Administration (Medicare) records. For deceased cases, controls were selected from state mortality files with additional matching for year of death. Persons with a cause of death of a malignancy under study, or in Kansas and Nebraska, a malignancy of an ill-defined site, homicide, suicide, or legal intervention were excluded. A total of 4,203 controls (Nebraska: 831 men, 824 women; Kansas: 1,005; Iowa/Minnesota: 1,543) were identified.

Interviews

Interviews were conducted with the subjects, or their next-of-kin if the subjects were deceased or incapacitated. The interviews were done by telephone in Nebraska and Kansas and in-person in Iowa/Minnesota. In Nebraska, 385 cases (201 men, 184 women) and 1,432 controls (725 men, 707 women) were interviewed, yielding interview response rates of 91 percent for male cases, 89 percent for female cases, 87 percent for male controls, and 86 percent for female controls. The overall response rate for controls, which accounted for the 91 percent response rate in the household census phase of the RDD procedure, was 85 percent for men and 84 percent for women. In Kansas, 170 cases and 948 controls were interviewed, yielding interview response rates of 96 percent and 94 percent, respectively. The RDD household census had a 92.3 percent response rate which made the overall control response rate 90 percent. In Iowa/Minnesota, 780 presumptive NHL cases were ascertained and 694 (89 percent) were interviewed. After pathology review of the interviewed cases, 622 were confirmed as NHL. Interviews also were obtained from 1,245 controls (81 percent) in Iowa/Minnesota. The overall response rate for controls, accounting for the 87.5 percent household census response rate, was 78 percent. Combining the three studies, interviews were obtained from 1,177 eligible cases (993 men, 184 women) and 3,625 controls (2,918 men, 707 women). Fourteen male controls were excluded from the analyses in this report because of missing data.

In each study, the interviews contained detailed questions on tobacco use including: the use of cigarettes; age or calendar year the person started smoking; the number of years of smoking (Kansas) or the age or calendar year the person stopped smoking (Nebraska and Iowa/Minnesota); average number of cigarettes per day; use of cigars or pipes; and use of smokeless tobacco. Because not all of the studies collected detailed information on intensity and duration of non-cigarette tobacco products, those data will not be presented. The interviews also included other potential risk factors for non-Hodgkin's lymphoma, such as a family history of cancer, employment as a farmer, pesticide use, occupational exposures, and medical conditions, with some variation across the three studies.

Risk measurement

The measure of association was the odds ratio (OR). Combining the subjects from the three studies, risk estimates for tobacco use were adjusted for age (20-44, 45-64, 65-74, 75+), gender, and state (Nebraska, Kansas, Iowa, Minnesota) by stratification. The source of the interview, *i.e.*, study subjects themselves *cf* proxy respondents, was found to be a negative confounder in these data and was added as a stratification factor. Adjustment for ever having lived or worked on a farm did not change risk estimates and is not presented in this report. Maximum likelihood estimates of the overall risk and 95 percent confidence intervals (CI) were computed by Gart's method.[29] For duration and intensity-response relationships, significance was assessed by means of Mantel's one-tailed linear trend test.[30]

Results

Table 2 presents the ORs for NHL by characteristics of tobacco use for all subjects combined and by respondent type. Overall, there was no association between NHL and any tobacco use or cigarette smoking. Risk appeared to decrease slightly with increasing intensity and duration of smoking, primarily due to the negative associations among subjects represented by proxy respondents. Analyses based on living subjects alone showed an excess of borderline significance among current smokers, but no exposure-response gradients were observed.

The role of smoking in the development of NHL appeared to differ by gender (Table 3). While there appeared to be little or no association in men, particularly among subject respondents, NHL was associated with smoking among women. Among the female subject respondent smokers, NHL was increased about twofold. However, the exposure-response gradients, although statistically significant, were inconsistent and generally diminished in the highest category. The ORs were similar for exposure-response gradients among ex- and current smokers (data not shown).

Table 2. Number of non-Hodgkin's lymphoma (NHL) cases and controls and odds ratios (OR) for tobacco use by respondent type in Eastern Nebraska, Kansas, Iowa, and Minnesota

Tobacco use	Total				Direct subject respondents				Proxy respondents			
	NHL	Controls	OR	(CI)[a]	NHL	Controls	OR	(CI)[b]	NHL	Controls	OR	(CI)[b]
No tobacco use	356	1,179			221	753			135	426		
Ever used tobacco	820	2,424	1.0	(0.8-1.1)	516	1,330	1.1	(0.9-1.4)	304	1,094	0.7	(0.6-1.0)
Unknown	1	8	—	—	0	3	—	—	1	5	—	—
Cigarette smokers	726	2,164	1.0	(0.8-1.1)	467	1,203	1.1	(0.9-1.4)	259	961	0.7	(0.6-1.0)
Ex-smokers	371	1,134	0.9	(0.7-1.1)	257	712	1.0	(0.8-1.3)	114	422	0.7	(0.5-1.0)
Current	308	850	1.1	(0.9-1.3)	203	476	1.3	(1.0-1.6)	105	374	0.8	(0.5-1.1)
Unknown[c]	47	180	—	—	7	15	—	—	40	165	—	—
Cigarettes per day												
1-9	99	253	1.1	(0.8-1.4)	58	157	1.0	(0.7-1.5)	41	96	1.2	(0.7-1.8)
10-19	136	353	1.1	(0.9-1.5)	93	206	1.3	(1.0-1.8)	43	147	0.8	(0.5-1.3)
20	251	753	0.9	(0.8-1.2)	178	451	1.1	(0.9-1.5)	73	302	0.6	(0.4-0.9)
21+	210	693	0.8	(0.6-1.0)	135	377	0.9	(0.7-1.2)	75	316	0.6	(0.4-0.9)
Unknown	30	112	—	—	3	12	—	—	27	100	—	—
Chi; *P*-value for trend[d]			-1.8; 0.04				0.3; 0.4				-3.5; < 0.0001	
Years smoked												
1-10	79	230	1.2	(0.8-1.6)	56	178	1.1	(0.7-1.6)	23	52	1.4	(0.8-2.5)
11-20	101	294	1.1	(0.8-1.5)	69	211	1.0	(0.7-1.5)	32	83	1.2	(0.7-2.1)
21-30	120	316	1.1	(0.8-1.4)	85	219	1.0	(0.7-1.4)	35	97	1.2	(0.7-2.0)
31-40	136	402	0.8	(0.6-1.1)	97	231	1.1	(0.8-1.5)	39	171	0.5	(0.3-0.8)
41+	244	751	0.9	(0.7-1.1)	153	349	1.1	(0.8-1.5)	91	402	0.6	(0.4-0.8)
Unknown	46	171	—	—	7	15	—	—	39	156	—	—
Chi; *P*-value for trend[d]			-1.3; 0.1				1.1; 0.1				-3.6; < 0.0001	
Pack-years												
< 15	159	456	1.1	(0.8-1.4)	108	321	1.1	(0.8-1.4)	51	135	1.1	(0.7-1.7)
15 - < 35	186	511	1.1	(0.8-1.3)	139	343	1.2	(0.9-1.6)	47	168	0.8	(0.5-1.2)
35 - < 55	169	474	0.9	(0.7-1.1)	123	293	1.0	(0.8-1.4)	46	181	0.6	(0.4-1.0)
55 - 155	148	497	0.8	(0.6-1.0)	89	222	0.9	(0.7-1.3)	59	275	0.5	(0.3-0.8)
Chi; *P*-value for trend			-1.7; 0.04				0.6; 0.3				-3.6; < 0.0001	

[a] Odds ratio (95 percent confidence interval) adjusted for age, gender, state, and respondent type, compared with nonusers of tobacco.
[b] Odds ratio (95 percent confidence interval) adjusted for age, gender, and state, compared to nonusers of tobacco.
[c] Some smokers could not be classified as ex- or current smokers because of missing values for either age started or years of smoking, variables used to impute current smoking status in the Kansas study.
[d] Trend tests do not include the unknown category.

Among men, there was no evidence for a role of tobacco in follicular lymphoma (OR = 1.0, CI = 0.7-1.3) (Table 4). Smokers had a slightly decreased risk of diffuse lymphoma (OR = 0.8, CI = 0.6-1.0) and small lymphocytic lymphoma (OR = 0.7, CI = 0.5-1.1), and an increased risk of the remaining types of NHL (OR = 1.4, CI = 1.0-2.1). No consistent exposure-response gradients were observed (data not shown). These relationships were not changed when analyses were restricted to interviews supplied directly by subjects.

Among women, tobacco users had nonsignificant increased risks of follicular, diffuse, and small lymphocytic lymphoma (Table 4). Analyses of detailed smoking characteristics were limited by small numbers of exposed female cases, but showed greater risks for these three histologic types of NHL among current smokers than among ex-smokers. Risk for follicular and, to a greater extent, small lymphocytic lymphoma appeared to increase with years smoked ($P = 0.02$), based on small numbers (data not shown). Female smokers generally had no greater risk of other histologic types of NHL than nonsmokers.

Other forms of tobacco showed no association with NHL, whether used alone or in combination with each other. Persons who ever smoked pipes or cigars had an OR of 0.9 (CI = 0.7-1.1) for NHL. Smokeless tobacco users had an OR of 1.0 (CI = 0.7-1.2). Among persons who used only one type of tobacco, the pipe or cigar

Table 3. Number of non-Hodgkin's lymphoma (NHL) cases and controls and odds ratios (OR) for tobacco use by gender and respondent type in Eastern Nebraska, Kansas, Iowa, and Minnesota

Tobacco use	Men								Women							
	Total respondents[a]				Direct subject respondents				Total respondents[a]				Direct subject respondents			
	NHL	Controls	OR	(CI)[b]	NHL	Controls	OR	(CI)	NHL	Controls	OR	(CI)	NHL	Controls	OR	(CI)
No tobacco use	240	685	—	—	154	434	—	—	116	494	—	—	67	319	—	—
Ever used tobacco	752	2,216	0.9	(0.7-1.1)	1,203	1,203	1.0	(0.8-1.2)	68	208	1.3	(0.9-1.9)	50	127	1.9	(1.2-3.0)
Unknown	1	3	—	—	0	0	—	—	0	5	—	—	0	3	—	—
Cigarette smokers	658	1,957	0.9	(0.7-1.1)	417	1,076	1.0	(0.8-1.2)	68	207	1.3	(0.9-1.9)	50	127	1.9	(1.2-3.0)
Ex-smokers	350	1,054	0.9	(0.7-1.1)	238	660	0.9	(0.7-1.2)	21	80	1.0	(0.6-1.9)	19	52	1.7	(0.9-3.3)
Current	269	746	1.0	(0.8-1.2)	175	402	1.1	(0.9-1.5)	39	104	1.5	(0.9-2.4)	28	74	1.9	(1.1-3.3)
Unknown[c]	39	157	—	—	4	14	—	—	8	23	—	—	3	1	—	—
Cigarettes per day																
1-9	86	194	1.1	(0.8-1.5)	48	114	1.0	(0.7-1.6)	13	59	0.9	(0.5-1.9)	10	43	1.1	(0.5-2.5)
10-19	115	318	1.0	(0.7-1.3)	80	182	1.2	(0.8-1.7)	21	35	2.5	(1.3-4.8)	13	24	2.9	(1.3-6.5)
20	229	690	0.9	(0.7-1.1)	157	414	1.0	(0.7-1.3)	22	63	1.3	(0.7-2.3)	21	37	2.7	(1.4-5.3)
21+	203	652	0.8	(0.6-1.0)	130	356	0.9	(0.7-1.2)	7	41	0.5	(0.2-1.3)	5	21	1.1	(0.3-3.4)
Unknown	25	103	—	—	2	10	—	—	5	9	—	—	2	2	—	—
Chi; *P*-value for trend[d]			-2.2; 0.02				-0.7; 0.3				0.7; 0.3				2.9; 0.002	
Years smoked																
1-10	73	191	1.2	(0.9-1.8)	53	149	1.2	(0.8-1.7)	6	39	0.8	(0.3-2.0)	3	29	0.6	(0.1-2.4)
11-20	93	270	1.1	(0.8-1.4)	62	192	1.0	(0.7-1.4)	8	24	1.5	(0.5-3.8)	7	19	1.8	(0.6-5.0)
21-30	113	287	1.1	(0.8-1.4)	79	198	1.0	(0.7-1.4)	7	29	1.0	(0.4-2.6)	6	21	1.5	(0.5-4.2)
31-40	118	371	0.7	(0.6-1.0)	80	212	0.9	(0.6-1.2)	18	31	1.9	(1.0-3.9)	17	19	3.7	(1.7-8.4)
41+	223	690	0.8	(0.7-1.0)	139	311	1.0	(0.8-1.4)	21	61	1.2	(0.7-2.1)	14	38	1.7	(0.8-3.4)
Unknown	38	148	—	—	4	14	—	—	8	23	—	—	3	1	—	—
Chi; *P*-value for trend[d]			-2.2; 0.02				-0.1; 0.4				1.7; 0.04				3.1; 0.001	
Pack-years																
< 15	144	384	1.1	(0.8-1.4)	96	265	1.0	(0.8-1.4)	15	72	0.9	(0.5-1.8)	12	56	1.1	(0.5-2.4)
15 - < 35	163	460	1.0	(0.7-1.2)	120	305	1.0	(0.8-1.4)	23	51	1.8	(1.0-3.3)	19	38	2.5	(1.3-4.8)
35 - < 55	154	439	0.8	(0.6-1.1)	110	273	0.9	(0.7-1.2)	15	35	1.5	(0.7-3.0)	13	20	2.9	(1.2-6.9)
55 - 155	143	475	0.8	(0.6-1.0)	86	212	0.9	(0.7-1.3)	5	22	0.6	(0.2-1.9)	3	10	1.3	(0.3-5.2)
Chi; *P*-value for trend			-2.2; 0.01				-0.5; 0.3				1.1; 0.1				3.0; 0.001	

[a] Total respondents includes subject respondents and proxy respondents.
[b] Odds ratio (95 percent confidence interval) adjusted for age, state, and respondent type, compared with non-tobacco users.
[c] Some smokers could not be classified as ex- or current smokers because of missing values for either age started or years of smoking, variables used to impute current smoking status in the Kansas study.
[d] Trend tests do not include the unknown category.

Table 4. Number of non-Hodgkin's lymphoma (NHL) cases and controls and odds ratios (OR) for tobacco use by histologic type[a] and gender in Eastern Nebraska, Kansas, Iowa, and Minnesota

Tobacco use	Follicular				Diffuse			Small lymphocytic			Other		
	NHL	Controls	OR	(CI)[b]	NHL	OR	(CI)	NHL	OR	(CI)	NHL	OR	(CI)
Men													
No tobacco use	685	69	—	—	100	—	—	32	—	—	37	—	—
Ever tobacco use	2,216	216	1.0	(0.7-1.3)	268	0.8	(0.6-1.0)	80	0.7	(0.5-1.1)	188	1.4	(1.0-2.1)
Unknown	3	0	—	—	1	—	—	0	—	—	0	—	—
Cigarette smokers	1,957	191	1.0	(0.7-1.3)	237	0.8	(0.6-1.0)	61	0.6	(0.4-1.0)	169	1.4	(1.0-2.1)
Ex-smokers	1,054	99	0.9	(0.6-1.2)	134	0.8	(0.6-1.1)	37	0.6	(0.4-1.0)	80	1.2	(0.8-1.9)
Current	746	88	1.1	(0.8-1.7)	88	0.8	(0.5-1.1)	22	0.7	(0.4-1.3)	71	1.7	(1.1-2.7)
Unknown[c]	157	4	—	—	15	—	—	2	—	—	18	—	—
Women													
No tobacco use	494	35	—	—	40	—	—	4	—	—	36	—	—
Ever used tobacco	208	20	1.3	(0.7-2.5)	27	1.6	(0.9-2.8)	5	3.4	(0.7-16.0)	16	0.9	(0.4-1.8)
Unknown	5	0	—	—	0	—	—	0	—	—	0	—	—
Cigarette smokers	207	20	1.3	(0.7-2.5)	27	1.6	(0.9-2.8)	5	3.4	(0.7-16.0)	16	0.9	(0.4-1.8)
Ex-smokers	80	6	0.9	(0.3-2.3)	7	1.1	(0.4-2.8)	2	3.1	(0.4-21.4)	6	0.9	(0.3-2.4)
Current	104	12	1.4	(0.6-3.0)	16	1.9	(0.9-3.9)	3	3.8	(0.6-22.3)	8	0.9	(0.3-2.2)
Unknown[c]	23	2	—	—	4	—	—	0	—	—	2	—	—

[a] Histology: Follicular (Working Formulation B-D, diffuse (Working Formulation E-G), small lymphocytic (Working Formulation A), other (Working Formulation H-J and miscellaneous).
[b] Odds ratio (95 percent confidence interval) adjusted for age, state, and respondent type, compared to nonusers of tobacco.
[c] Some smokers could not be classified as ex- or current smokers because of missing values for either age started or years of smoking, variables used to impute current smoking status in the Kansas study.

smokers had an OR of 1.0 (CI = 0.6-1.4) and users of smokeless tobacco had an OR of 0.8 (CI = 0.4-1.3). Persons who used all forms of tobacco (*i.e.*, cigarettes, pipes, or cigars, and smokeless tobacco) at some time during their lives had an OR of 0.9 (CI = 0.6-1.3).

Family history of cancer did not significantly modify the risk of NHL associated with smoking.

Discussion

This combined analysis of data from three population-based case-control studies was based on approximately 1,200 cases and 3,600 controls. A total of 726 cases and 2,164 controls smoked cigarettes, making this study far larger than any single study previously published on NHL and tobacco use. Overall, there was no association with cigarette smoking or use of other forms of tobacco. A slight negative association evident in the analyses by intensity and duration of smoking was not present when analyses were restricted to information obtained directly from living subjects. Proxy respondents for deceased cases and matched deceased controls showed significantly decreased risks of NHL, probably due to the inclusion of controls with smoking-related causes of death.[31] While it would be possible to exclude known smoking-related causes of death from the deceased controls for reanalysis, McLaughlin *et al*[31] have reported that such exclusion reduces but does not eliminate the excess of cigarette smokers among deceased controls. For smoking, it would be better to base this study's conclusions on the living subjects only.

There was a suggestion of a positive association between smoking and NHL among women, but not men. It is difficult to postulate a gender-specific causal association for smoking. However, there is some evidence that women smokers incur a greater risk of lung cancer than men who smoke similar amounts.[32-34] In the present study, there were no clear exposure-response gradients, and the association among women may be due to chance. On the other hand, a lack of an exposure-response gradient also was observed in a study of smoking and leukemia[35] for which the relationship is more clearly established. Smoking is known to have effects on the immune system including alterations in T-cell subsets, elevated white blood counts, and lower percentages of natural killer cells.[36-40] Immunodeficiencies and immunosuppresion, both genetic and acquired, are strong risk factors for NHL.[41-42] Most previous studies of NHL and smoking have consisted of men only[1,3-5,9-11] or presented results for men and women combined.[6-8] Williams and Horm[2] reported nonsignificant increases of some types of lymphoma among women in the highest cigarette smoking

level based on small numbers of cases. Additional data on smoking and NHL among women are needed.

If smoking were related causally to NHL among women, the increase in smoking among women in recent decades[43] might explain some of the 57 percent increase among women in the incidence of NHL over the past 20 years.[44] Most other known and postulated causes of NHL, such as human immunodeficiency virus, pesticides, and solvents, are more prevalent among men than women.[45-47] The agents responsible for the rising incidence of NHL might differ among men and women. Cigarette smoking and other factors, such as use of hair coloring products,[23,48] may be responsible for the rise in women, but play little or no role among men.

This large case-control study provides strong evidence that smoking has little or no effect on the development of NHL among men. However, the possible role of smoking in the etiology of NHL among women needs further evaluation to determine if a gender-specific response may occur.

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